Global Regulatory Policy

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December 10, 2004

MERCK
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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: **Docket No. 04D-0377,** ICH E14, Clinical Evaluation of QT Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs
Docket No. 04D-0378, ICH S7B, Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Merck & Co., Inc. is a leading worldwide human health product company. Merck's corporate strategy — to discover new medicines through breakthrough research — encourages us to spend nearly $3 billion annually on worldwide Research and Development (R&D). Through a combination of the best science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical and biological products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R&D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by the draft guidances referenced above (hereafter referred to as the Guidances). We have experience in evaluating both the nonclinical and clinical potential for human pharmaceuticals to delay ventricular repolarization; therefore, we are well qualified to comment on these guidances.

We provide general comments, specific comments, and conclusions. In addition, we attach our responses to the items on which CHMP specifically requested input as they may be of interest to the FDA as well.

General Comments

Although ICH Guidances S7B and E14 are greatly improved since the concept stage, the two guidances need to be integrated to permit a coherent and logical approach to drug development. We commend the ICH Expert Working Group members for their efforts to address a complicated and evolving topic. Each guidance makes a seminal contribution to

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drug development. The S7B Guidance adds the necessary depth, breadth, and clarity to the previously established S7A Guidance by specifying the nonclinical evaluation of the potential for drugs to delay ventricular repolarization (QT interval prolongation). The E14 Guidance provides the standards for a robust clinical evaluation of the potential for drugs to delay ventricular repolarization. However, the S7B and E14 Guidances are not harmonized sufficiently.

Merck objects to the absolute requirement to conduct a thorough QT/QTc clinical study for all drugs in development. Merck supports the S7B Guidance; nonclinical testing is not only valuable, but critical to assess the potential risk for humans, to design appropriate clinical tests, and to interpret clinical data. Merck is not aware of any drug with a completely clean nonclinical S7B assessment (or an assessment with a large margin between the expected clinical exposure and the exposure at which there is a nonclinical cardiovascular safety signal) that has caused Torsade de Pointes or prolonged QT in the clinic[1]. As such, Merck completes a detailed nonclinical risk assessment prior to first administration of a compound to humans[2]. However, the strength and clarity of S7B is lost in the context of E14 where there are numerous inconsistencies with regard to the value of the nonclinical risk assessment as outlined in S7B. The nonclinical evaluation outlined in S7B should be recommended for all development candidates that are systemically absorbed. A thorough QT/QTc clinical study should be required for any development candidate with a nonclinical signal indicative of the potential for prolongation of ventricular repolarization in a range of exposures near projected clinical exposures. A thorough QT/QTc clinical study should not be routinely required for all drugs. For development candidates that lack a nonclinical signal[3], it should be sufficient to collect ECGs during Phase I studies evaluating a range of doses and from a subset of patients during the clinical program.

The E14 Guidance indicates there are regional differences in whether nonclinical data are considered informative about assessing risk of QT/QTc prolongation in humans. This implies that there will be regional differences in the scientific standards used to interpret nonclinical data and implications for human safety. This is inconsistent with the goal of harmonization, and makes it difficult for a sponsor to develop a drug for registration in all

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[1] Merck drug candidates and marketed products with no evidence of a nonclinical QT signal have never been associated with Torsade de Pointes or QT/QTc interval prolongation in humans. Merck has advanced only three development candidates with a nonclinical QT signal into clinical trials. From phase 1 studies of each of these candidates, QT/QTc interval prolongation was confirmed to be present in humans at exposures predicted from nonclinical *in vivo* QT/QTc assay results. Merck's experience is consistent with the literature (Redfern et al, 2003, included as Attachment 1) and the findings in the prospective studies performed by the ILSI/HESI Cardiovascular Safety Subcommittee and the PRODACT (JPMA) project using drugs known to cause Torsade de Pointes and drugs believed not to cause Torsade de Pointes or prolong QT/QTc in humans.

[2] Consistent with the S7B Draft Guidance, this risk assessment is made prior to the first administration of the drug to humans and is refined when the following clinical data are available: (1) determination of exposure required for therapeutic benefit, and (2) results from clinical investigations of the risk for QT/QTc interval prolongation at multiples of the therapeutic exposure.

[3] At Merck, a development candidate that lacks a nonclinical QT signal is defined as one that is inactive in an ion channel assay at concentrations >30-fold above predicted clinical exposure when tested with concentrations at the maximum solubility, and more importantly, does not increase QT/QTc intervals in any *in vivo* QT assay at exposures >30-fold above the targeted therapeutic exposure in humans (Redfern et al, 2003, included as Attachment 1).

ICH regions unless the sponsor defaults to a conclusion that nonclinical data have no role in human risk assessment.

<u>Specific Comments</u>

We recommend the following topics be further addressed prior to the issuance of the final guidances:

1. The E14 Guidance is inconsistent regarding the predictive value of nonclinical data to assess the risk of QT prolongation in humans.

In general, E14 places little emphasis on nonclinical testing to assess the risk of QT prolongation in humans, as evidenced by the following statements:

- The predictive value of nonclinical testing to exclude the risk for QT prolongation is termed "controversial." (E14, Line 154)
- This results in a recommendation that sponsors conduct a thorough clinical QT study "in almost all cases for regions where nonclinical data are not considered able to preclude risk of QT/QTc prolongation." (E14, Lines 154-156)
- A "negative (= clean) thorough (clinical) QT/QTc study, even in presence of nonclinical data of concern, will permit sponsors to collect on-therapy ECGs in accordance with the current practices . . .". (E14, Lines 166-168)

However, the following statements in E14 suggest there is value in nonclinical testing, in conflict with the statements above:

- The "failure to perform adequate <u>nonclinical and</u> clinical assessments of the potential QT/QTc interval prolonging properties of a drug can likewise be justification to delay or deny marketing authorization." (E14, Lines 621-623)
- The stated objective of S7B, is that nonclinical studies ". . .can be used to elucidate the mechanism of action and, when considered with other information, estimate risk for delayed ventricular repolarization and QT prolongation in humans." (S7B, Lines 66-68) This statement is consistent with E14, Lines 621-623 implying the need for adequate nonclinical assessments of QT prolongation. However, it is inconsistent with the overall tone of E14 throughout which nonclinical testing is secondary to clinical evaluation.

<u>Recommendation</u>: The Guidances should consistently acknowledge the value of nonclinical assessments as opportunities to effectively assess potential risk to study subjects, maximize the value of clinical data, and develop safer drugs.

2. The S7B Guidance is inconsistent with regard to the timing of nonclinical studies in relation to clinical studies.

There appear to be inconsistencies between having established that there is a measure of value in conducting the nonclinical studies (S7B, Lines 66-68), and the statements regarding the timing of nonclinical studies, as evidenced by the following statements:

- "Results from S7B nonclinical studies. . . . generally do not need to be available prior to first administration in humans. However, these results .... can support the planning and interpretation of subsequent clinical studies. The early availability of these data is considered valuable." (S7B Lines 162-166)

- "In circumstances where results among nonclinical studies are inconsistent and/or results of clinical studies differ from those of nonclinical studies, retrospective evaluation and follow-up nonclinical studies can be used to understand the basis for the discrepancies. Results from follow-up studies can be a significant component of an integrated risk assessment." (S7B, Lines 126-129)
- "The integrated risk assessment should be provided for the Investigator's Brochure (IB) and the Nonclinical Overview (ICH M4)," which could be interpreted to mean that the nonclinical results must be available prior to studies in humans, when the first edition of the IB is written (S7B, Lines 149-151).

<u>Recommendation</u>: *Sponsors should be required to complete an in vivo QT study, in the appropriate species <u>prior</u> to Phase I trials in humans. There is value in conducting nonclinical studies to estimate and reduce the risk for QT prolongation in study subjects, therefore, we recommend editing S7B at Lines 162-166 of S7B to remove the option to conduct nonclinical QT studies <u>after</u> the first administration in humans. The initial nonclinical studies should be completed early enough to make additional "follow-up" studies relevant to clinical development.*

If the final Guidance mandates the conduct of an in vivo QT study prior to human trials, Section 2.3.6 should remain as is and state, "The integrated risk assessment should be provided for the Investigator's Brochure and the Nonclinical Overview (ICH M4)."

*If the final Guidance does not mandate the conduct of an in vivo QT study prior to human trials, Section 2.3.6 should state, "The integrated risk assessment should be provided for the Investigator's Brochure, **when available**, and the Nonclinical Overview (ICH M4)."*

3. **The scope of the E14 Guidance is not clear (refer to Section 1.3 at Line 144 and Section 2.1.2 at Line 269).**

As currently written, it is not clear to which products the recommendations apply. The recommendations appear to apply:

- To new drugs (assumed to mean those not yet approved) having systemic bioavailability;
- To approved drugs, when a new dose or route of administration is being developed; and
- When the agent is a member of a pharmacologic class.

A pharmacologic class is not a sufficient criterion to designate a compound as having a signal of potential risk. For example, antibiotics as a pharmacologic class do not have equal risks (e.g. a chemical subset of fluoroquinolone antibiotics versus all fluoroquinolone antibiotics versus all antibiotics). It is more accurate to replace "pharmacologic class" with "structurally/chemically similar."

<u>Recommendation</u>: *Section 1.3 should be simplified to state that the recommendations apply to all products that are systemically absorbed; this includes: (1) products that are not yet approved, and (2) approved products when changes are being made that alter the Cmax or AUC. Reference to "pharmacologic class" as a reason to apply the recommendations should be removed.*

Section 1.3 should read: "The recommendations contained in this document are generally applicable to new drugs having systemic bioavailability. The focus is on agents being developed for uses other than the control of arrhythmias, as antiarrhythmic drugs can prolong the QT/QTc interval as part of their mechanism of clinical efficacy. While this document is concerned primarily with the development of novel agents, the recommendations might also apply to approved drugs when a new dose or route of administration results in significantly higher Cmax or AUC. Additional ECG data might also be considered appropriate if a new indication or patient population were being pursued, ***but only if the exposure is expected to change or the population is at increased risk.*** *The evaluation of the effect of a drug on QT interval would also be considered important if the drug or members of its* ***chemical/structural*** ~~*or pharmacological*~~ *class has been associated with QT/QTc interval prolongation, TdP, or sudden cardiac death during clinical studies or post-marketing surveillance.*

Line 269 should read, "If an investigational drug belongs to a ***chemical/structural*** ~~*or pharmacologic*~~ *class that has been associated. . . ."*

4. **In general, the E14 Guidance does not adequately discuss situations in which a thorough QT study is not needed (e.g., drugs that are not systemically absorbed or drugs in which exposures are substantially greater than the therapeutic exposure have been well tolerated without a QTc signal).**

<u>Recommendation</u>: *A thorough QT study should be required for any development candidate with a nonclinical signal indicative of the potential for prolongation of ventricular repolarization in a range of exposures near projected clinical exposures. Merck objects to the absolute requirement to conduct a thorough QT study for all drugs in development. In addition, the Guidance should reflect that a thorough QT study is not needed for:*

- *Drugs which are not systemically absorbed or which have minimal systemic exposure (e.g. ophthalmic solutions)*
- *Drugs in which the expected therapeutic systemic exposure is extremely low relative to what has been safely administered to humans*
- *In some situations, sponsors will have demonstrated that there is no QTc signal at clinical exposures that are significantly greater (~ > 50 fold) than the expected therapeutic exposure in clinical studies where QT/QTc measurement is not confounded by other actions of the drug that prevent an effective assessment of QT/QTc interval*[4]*. This situation would typically occur in a rising single dose study for a well tolerated and safe drug prior to clear knowledge of the therapeutic exposure. In such a study, an active control would not have been administered. In this situation, if the mean difference between the drug and placebo (baseline-subtracted) for the QTc interval is < 8 ms, the utility of a thorough QT study at significantly lower exposures*

[4] The basic pharmacological principle is that the mechanism for QT interval prolongation associated with Torsade de Pointes has a dose-response relationship. By exploring doses well above the therapeutic dose and finding no changes in QT/QTc, it is extremely unlikely that there is a significant effect on repolarization at lower doses. The advantage of exploring doses well above the expected therapeutic exposure when there is a dose-response relationship is that the high sensitivity of the thorough QT/QTc study is not needed to make a valid assessment of risk. Exceptions to this would include drugs that when given at high concentrations confound the QT signal (e.g. marked changes in heart rate, effects on multiple ion channels); however, these findings would be readily apparent in clinical and nonclinical evaluations.

is questionable. In the absence of a positive control it would be possible that the study might have missed a small QT signal – however, it would be extremely unlikely that if there was a small QT signal at exposures 5 – 10 fold higher than the target therapeutic exposure, that signal would not have increased in magnitude at higher exposures and thus should have been easily detected at the highest exposure.

5. **Guidance E14 requires that "... the drug be tested at substantial multiples of anticipated maximum therapeutic exposure" (refer to Section 2.1.2, The Thorough QT/QTc Study: Dose-Effect and Time Course Relationships).**

In general, the thorough QT/QTc study should evaluate high exposures in humans, although it is unreasonable to routinely recommend that drugs be tested at substantial multiples of the anticipated maximum exposure. Drugs should be tested at appropriate multiples above the therapeutic exposure, as dictated by the pharmacokinetic profile of the compound, as well as the safety and tolerability of the compound as defined clinically. For compounds that are susceptible to metabolic inhibition, the effect of the drug on QT/QTc should be evaluated at exposures that would be anticipated in the presence of metabolic inhibition. In many cases, these exposures can be achieved by simply increasing the dose of the drug rather than administering the drug with a metabolic inhibitor. However, if absorption limits exposure, it would be appropriate to achieve high exposures by concomitant administration of a single metabolic inhibitor. Compounds that exhibit extremely variable exposures in humans should be tested at multiples above the anticipated maximum exposure to cover the potential wide range of exposures in large numbers of patients. In addition, it would be reasonable to test higher exposures for compounds that will be given to patients who may be particularly sensitive or vulnerable to the effects of prolonged ventricular repolarization. Demonstration of a concentration-response relationship would be useful in understanding the precise concentrations resulting in prolongation of ventricular repolarization.

Recommendation: *E14 Section 2.1.2 should be revised to read as follows: "An adequate drug development programme should ensure that the dose-response and generally the concentration-response relationship for QT/QTc prolongation have been characterized* ***in compounds that effect ventricular repolarization****, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses. Data on the drug concentrations around the time of ECG assessment would aid this assessment. If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at* ***appropriate*** *~~substantial~~ multiples of the anticipated maximum therapeutic exposure* ***as dictated by the pharmacokinetic profile of the compound****. Alternatively, if the concentrations of a drug can be increased by drug-drug or drug-food interactions involving metabolizing enzymes (e.g. CYP34A, CYP2D6) or transporters (e.g. P-glycoprotein), these studies* ***should evaluate the high exposures either using higher doses of the drug (if well tolerated and if absorption is not limiting) or*** *~~can be performed~~ under conditions of maximum inhibition* ***by a single route****. This approach calls for a detailed understanding of the absorption, distribution, metabolism and excretion of the drug. In general, the duration of dosing or dosing regimen should be sufficient to characterize the effects of the drug and its active metabolites at relevant concentrations.*

6. The E14 Guidance confuses the hypothesis to be tested and the decision rule/statistical method needed to address the hypothesis.

At Line 262, the draft Guidance states, "Based on similar considerations, a negative 'thorough QT/QTc study' is one where the largest time-matched mean difference between the drug and placebo (baseline-subtracted) for the QTc interval is around 5 ms or less, with a one-sided 95% confidence interval that excludes an effect >8.0 ms."

The Guidance should specify the research hypothesis to be supported by data from the thorough QT study (e.g., "The investigational drug on average does not prolong the QTc interval by more than 8 ms when compared to placebo at any of the time-points."). How this hypothesis is tested becomes a statistical methods issue (e.g., the upper bound of the 95% confidence interval is below 8 ms). This is important since it gives the sponsor a clear assertion (hypothesis) to prove, and makes clear the Type I error rate that is acceptable to regulatory agencies (e.g. 5%, as is implicit in the use of a 95% one-sided confidence interval).

The current requirement to observe a point estimate around 5 ms or less (at Line 262) does not address the hypothesis with any degree of certainty. It is vague from a scientific point of view and complicates the issue. For example, does a drug with a point estimate of 6 ms and an upper confidence limit of 7 ms represent greater or lesser risk than a drug with a point estimate of 3 ms and an upper confidence limit of 9 ms? We find the first scenario preferable as it proves the hypothesis that the investigational drug does not prolong the QTc interval by more than 8 ms, and does it with a false-positive rate of at most, 5%.

<u>Recommendation</u>: *The Guidance should simply state that the hypothesis to be supported is, "The investigational drug on average does not prolong the QTc interval by more than 8 ms when compared to placebo at any of the time-points. This could be tested by demonstrating that the upper bound of the 95% one-sided confidence interval for the placebo-corrected change in QTc interval is below 8 ms."*

We recommend that the requirement of a point estimate around 5 ms be dropped as it has no objective scientific basis and is unnecessary.

7. Guidance E14 does not address the statistical problem of multiplicity that stems from the requirement that multiple ECG time-points must meet the bounds in the primary hypothesis.

The draft Guidance seems to imply that multiple ECG time-points must meet the bounds in the primary hypothesis. This requirement may result in a significant reduction in the overall power of the study since the overall power would be determined from the power of each of the comparisons. For example, assuming that the power to detect a change in QTc at each time-point was 0.90, then the overall power in the study, assuming 10 independent or uncorrelated time-points, would be reduced to ~ 0.35 (0.9^{10}). Although the precise decrement in power associated with measuring additional time-points is dependent on the correlation between the different time-points during the day, the overall power will be a decreasing function of the number of time-points.

<u>Recommendation</u>: *The Guidance should encourage the reliance on related scientific information (e.g. thorough exploration of PK-PD relationship, trend-over-time analysis, understanding of active metabolites, etc.) to minimize the number of time-points to be tested without sacrificing the scientific rigor of the study. For example, 3 to 4 ECG time-points around t_{max} and 1 or 2 time-points to capture any delayed effect may, on balance, be better than risking an erroneous result derived from a study with inadequate power. All data collected should be presented; if other time-points are evaluated, they should be presented and summary statistics should be provided.*

8. The E14 Guidance appears to place more emphasis on generating individual correction formulae for each patient rather than using Bazett's and Fridericia's corrections.

The draft states (Lines 401-407), "Various correction formulae have been suggested, of which Bazett's and Fridericia's corrections are the most widely used. In early trials evaluating the effects of a new drug on the QT/QTc interval in healthy volunteers, designed to detect relatively small effects (*e.g.*, 5 ms), it is important to apply the most accurate correction available (*e.g.*, methods using individually-derived relationships between RR and QT intervals)."

Subsequently, the draft states (Lines 441-445), "Corrections for heart rate using individual subject data have been developed, applying regression analysis techniques to individual pre-therapy QT and RR interval data over a range of heart rates, then applying this correction to on-treatment QT values. These approaches are considered most suitable for the 'thorough QT/QTc study' and early clinical studies, where it is possible to obtain many QT interval measurements for each study subject."

The calculation of individual rate correction not only requires multiple baseline ECGs, but also requires substantial variability in the heart rate during these baseline ECGs in order to most accurately assess the relationship between QT interval and heart rate. For subjects without significant variability in heart rate, individual rate correction formula will not be robust. The stability and reproducibility of individual correction formulas must be assessed prior to recommending this method in regulatory guidance.

Ultimately, the rate correction formula for a given data set depends on the characteristics of the patients and the drug being studied and is especially important for drugs that affect heart rate. The success of any correction formula can be assessed by looking at the regression of QTc and heart rate. If the correction formula is effective, this regression should have a slope =0 indicating that there is no longer a relationship between QTc and heart rate. If the slope is not 0, then it would be reasonable to utilize alternative correction formulas.

<u>Recommendation</u>: *There remains considerable debate about the use of individual rate corrections; therefore, it should not be emphasized in Guidance.*

9. The E14 Guidance makes repeated reference to "baseline measurements" but does not acknowledge there are multiple acceptable definitions.

Throughout E14, repeated references are made to baseline measurements and to determining the "time-matched mean difference between the drug and placebo (baseline-subtracted) for the QTc interval" (Lines 263-264 and 473). Mention is also made of "time-matched" baseline measurements in order to reduce the variability due to diurnal variation in QT/QTc intervals. However, E14 does not speak to which baseline measurements to use, if a single day of "time-matched" baseline measurements is needed for all compounds, and if multiple baseline measurements are needed for each period in a cross-over study.

There are insufficient published data to support baseline measurements to minimize the within-day (diurnal) variability, the day-to-day variability, or the week-to-week variability. If a single day of time-matched baselines is obtained for a cross-over study, the "time-matched" mean difference between the drug and placebo (baseline-subtracted) for the QTc interval is clear, although the baseline measurements are dropped from the analysis given that the value is subtracted for both active and placebo groups. A statistically equivalent analysis would be to simply present the comparison of the difference between the QTc interval on active treatment and placebo without the accompanying collection of baselines.

The implication that a distinct baseline measurement is needed for each period in a crossover study adds to the complexity of the study without a clear scientific rationale. Use of period-specific baselines makes the analysis heavily dependent on additional assumptions about the nature of carry-over and period effects; repeated baseline measures can create analytical complexity if the values are not stable over the course of the study. For rapidly acting drugs, it may be more appropriate to use a pre-dose value as the baseline.

Recommendation: *The guidance should be flexible and provide information about the range of potentially acceptable definitions of baseline. We recommend that Lines 472-474 read as follows: "The effect of an investigational drug on QT/QTc interval should be made by comparing the difference between the QTc interval on active treatment and placebo over the collection period (e.g. hourly, weekly, and monthly). In some situations, sponsors may wish to define the comparison as a difference between the baseline-subtracted changes in QTc on active treatment and placebo. When baseline-subtracted changes in QTc are used in the primary analysis, the definition and justification for the choice of baselines should be discussed in the sponsor's protocol.*

10. It is unclear whether the assay sensitivity validation pertains to the process or the subjects, and how the positive control should be utilized to validate the assay.

Lines 251-253 state, "The confidence in the ability of the study to detect QT/QTc prolongation can be greatly enhanced by the use of a concurrent positive control group to establish assay sensitivity." There are two areas of ambiguity within this sentence:

- Is "concurrent" positive control group meant to imply within a certain time frame (a few weeks or months of the study) or within the "thorough QT study"?
- Is the assay sensitivity a validation of the subjects, the process, or both?

If the assay validation is to make sure that the subjects in a given study have an increase in QTc in response to the positive control, then all subjects in a "thorough QT study" need to demonstrate a sufficient response to the positive control. This is not necessary given the consistent results reported from a large and expanding published experience with a positive control (e.g., moxifloxacin) given to healthy subjects. All subjects should not have to demonstrate a response to the positive control during the "thorough QT study."

If the assay validation is to focus on the process rather than the subjects, it could be done in a subset of patients. Validation of assay sensitivity should appropriately focus on two important elements, the method of collection ECG data, and the ECG core lab interpretation of the ECGs. There are important advantages to designing an assay validation portion of the study that is separate from the assessment of the effect of a drug on QT.

- Performing the validation of assay sensitivity prior to assessing the effect of a drug on QT/QTc allows the sponsor to make sure that the assay is validated prior to exposing subjects to high doses of investigational drug.
- The validation assay would require significantly less blood draws and fewer ECG time-points since the pharmacokinetics of a positive control (e.g., moxifloxacin) are well defined.

Although sponsors could conduct a thorough QT/QTc study with a 4 arm crossover design (placebo, low dose active, high dose active, control), the positive control could be given as part of a smaller 2-period crossover study completed prior to the initiation of the 3-period crossover study (placebo, low dose, high dose). Validation of assay sensitivity should be based on the pharmacokinetic profile of the positive control and the sample size should be calculated based on testing the hypothesis that the positive control is associated with an approximately 5 ms increase compared to placebo. This validation of the assay sensitivity could be done as an open-label study with individuals interpreting ECGs blinded to allocation to the positive control.

<u>Recommendation</u>: *The text on Lines 252-254 should be replaced with: "The ability to detect QT/QTc prolongation can be enhanced by validation of the sensitivity of the assay with a positive control. Given the experience with a positive control (e.g., moxifloxacin) in healthy subjects, the validation of the assay should focus on the methods for collecting ECG data and interpreting the QT interval. Agents other than a positive control (or maneuvers) could be used if there are sufficient data demonstrating their effect on QT/QTc in appropriate populations. The validation study could be performed as an open-label study, although it is imperative that the persons interpreting the ECGs be blinded to treatment allocation.*
As experience is gained with the conduct of "thorough QT studies", it may be possible to validate assay sensitivity periodically, not in every study, provided the methods are validated. The guidance should allow for a reconsideration of the assay validation process in the future. For example, if an investigative site is doing a few QT/QTc studies over the course of a few months with an established central ECG laboratory, it should not be necessary for each of the studies to establish validation of assay sensitivity. A single dedicated study performed periodically by the site and the central ECG lab should be sufficient to assure that the study will detect modest QT/QTc prolongation. This approach results in exposing fewer subjects to the positive control and may decrease drug development timelines.

<u>Conclusions</u>

We recommend that the following issues be addressed when finalizing the ICH Guidances S7B and E14.

1. The guidances should be harmonized to permit a coherent and logical approach to drug development. Particular attention should be paid to:

- The value of nonclinical assessments as opportunities to effectively assess potential risk to study subjects, maximize the value of clinical data, and develop safer drugs.
- Completion of an in vivo QT study, in the appropriate species prior to Phase I trials in humans.
- The elimination of regional differences in the scientific standards used to interpret nonclinical data and its implications for human safety.

2. A thorough QT/QTc clinical study should not be routinely required for all drugs.

- A thorough QT study should be required for any development candidate with a nonclinical signal indicative of the potential for prolongation of ventricular repolarization in a range of exposures near projected clinical exposures.
- For development candidates that lack a nonclinical signal, it should be sufficient to collect ECGs during Phase I studies evaluating a range of doses and from a subset of patients during the clinical program.
- Rather than testing drugs at substantial multiples of the anticipated maximum exposure, drugs should be tested at appropriate multiples above the therapeutic exposure as dictated by the pharmacokinetic profile of the compound.
- The recommendations should apply to all products that are systemically absorbed including: (1) products that are not yet approved, and (2) approved products when changes are being made that alter the Cmax or AUC.
- Reference to "pharmacologic class" as a reason to apply the recommendations should be removed.

3. The following statistical points should be addressed:

- The hypothesis to be supported is, "The investigational drug on average does not prolong the QTc interval by more than 8 ms when compared to placebo at any of the time-points."
- The requirement of a point estimate around 5 ms should be dropped.
- Sponsors should rely on related scientific information to minimize the number of time-points to be tested.
- Individual rate corrections should not be emphasized.
- There is a range of potentially acceptable definitions of baseline.
- The validation of the assay should focus on the methods for collecting ECG data and interpreting the QT interval.

We welcome the opportunity to comment on these draft Guidances and to meet with you to discuss these issues. Please feel free to contact me at (301) 941-1403.

Sincerely,

Lauren M. Hetrick

Lauren M. Hetrick
Director, Regulatory Policy

Attachments:

1 – Redfern WS, Carlsson et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de points for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovascular Research 2003; 58:32-45.

2 - Responses to CHMP Topics